Correspondence

Careless talk costs grants

Alan Akers

The editors of *Current Biology* really should be more careful; some contributors are in danger of giving the game away. Years of careful fostering of the idea that everything can be explained in terms of molecular genetics and structural biology — thus keeping many of us gainfully employed — may have been undermined by their careless revelations. The current ascendancy of these disciplines could be at risk if information so casually made available should fall into the wrong hands.

Usually, you play your role exceptionally well. Unqualified assertions that genetic studies of aggressiveness in mice could "…be directly applicable to our understanding of human nature" slipped into the literature without a ripple [1]. Sydney Brenner's suggestion that, because some viral gene products combine in a fixed proportion, "it is possible to encode a mathematical rule in DNA" [2] — with the logical extrapolation that if he, a mere bundle of gene products, jumped out of the window, his DNA would implicitly encode the law of gravity — gave genome studies the opportunity to annex half the funds for chemical and physical research. Then there was the statement about the yeast genome, worthy of a Star Trek script, "…it encourages us to pursue the goal that has been implicit from the beginning: the complete understanding of how a eukaryotic cell functions. The attainment of this lofty goal now seems possible" [3].

Virtual biology and surfing the genomes was all set to abolish the need for messy, wet experiments, which don't always work and, when they do, have a regrettable tendency to throw up untidy, unexpected results. Many of us were looking forward to seeing out our entire research careers with a few clicks on the mouse and a sheaf of publications liberally seeded with comments such as 'intriguing conserved sequence motif', 'could suggest', 'might imply' and (my favourite) 'putative receptor'.

But, just when half the world was convinced that every problem from constipation to criminality is rooted in the base sequence of DNA, you allow loose talk such as "…almost any protein domain can bind inositol phosphate if required" [4] to slip through. Furthermore, the authors openly admit to "…the variety of domains that can bind inositol phosphates", and make things even worse by conceding that "…the functions of most of the binding sites are not yet clear".

Every research scientist using low molecular weight, biologically active compounds soon becomes aware that almost any protein domain can bind almost anything under the right circumstances, but most are instinctively discreet about it. If the promiscuous tendencies of proteins and the sheer variability of biological systems became widely appreciated, ignorant, unscrupulous journalists could call into question our ability to predict the behaviour of living systems from their DNA sequences and protein structures. The fig-leaf of *a priori* reasoning could be shamelessly stripped away to reveal vulgar *post hoc* rationalization.

We can only hope that the relaxed style of *Current Biology* and the speculative license it allows to its contributors have not attracted critical readers from outside the profession.

References

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Warthog and Groundhog, novel families related to Hedgehog

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Cell–cell signalling is one of the fundamental mechanisms by which different cell fates are generated during development. One group of signalling molecules, encoded by the *Drosophila* gene *hedgehog* and its vertebrate orthologues, has been shown to play important roles during development of flies and vertebrates (see [1–3]). Searching through the *Caenorhabditis elegans* genome, a major fraction of which has now been sequenced [4], reveals several sequences with similarities to *hedgehog* genes. The similarity is restricted to the carboxyl terminus of the Hedgehog proteins, which is surprising given that the amino-terminal part, which provides the biologically active signal, is more highly conserved between fly and vertebrate Hedgehogs. The carboxyl terminus is a distinct domain that has autoproteolytic activity and cleaves Hedgehog into a protease domain and a signalling part [5–7], and it is thought to regulate the release of the amino-terminal signal (see [8]).

The carboxy-terminal domain, which I refer to here as the 'Hog' domain, is about 200–250 amino acids long. Figures 1 and 2a show an alignment of the Hog domains of various Hedgehogs from flies and vertebrates, as well as the predicted products of several of the new *C. elegans* genes. The level of sequence similarity between the *C. elegans* and Hedgehog sequences is of the order of 22–32 % identity in this domain, with highly significant scores produced by BLAST database searches [9]. The probability of a chance match of the ZK678 Hog domain to *Drosophila* Hedgehog is 4.2×10^{-7}. A search of Genbank with the Hog domain has not revealed